EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment to the claims was given in a telephone interview with Robert Murray on 08/03/2009.

Authorization for this examiner's amendment to the specification was given in a telephone interview with Monica Kitts on 09/01/2009.

The application has been amended as follows:

IN THE CLAIMS:

6. A method for treating damage to bone, cartilage, connective tissues, skin, mucous membranes[[,]]or epithelium ~~or teeth~~, comprising administering a protein of the TGFβ family, wherein said protein is encoded by a DNA molecule which comprises a sequence selected from the group consisting of:

(a) the sequence shown in SEQ ID NO: 1,

(b) a part of SEQ ID NO: 1 which ~~encodes~~ comprises nucleotides 1783-2142 and encodes the mature protein,

(c) a nucleotide sequence which encodes the amino acid sequence according to SEQ ID NO: 2, and

(d) a nucleotide sequence which encodes the mature protein with amino acids 382-501 according to SEQ ID NO: 2,

to a patient in need of such treatment.

Cancel claims 7–9.

10. A method for treating damage to connective tissues, skin, mucous membranes, or epithelium or for use in connection with dental implants, comprising administering a protein of the TGFβ family, wherein said protein is encoded by a DNA molecule which comprises a sequence selected from the group consisting of:

(a) the sequence shown in SEQ ID NO: 1,

(b) a part of SEQ ID NO: 1 which ~~encodes~~ comprises nucleotides 1783-2142 and encodes the mature protein,

(c) a nucleotide sequence which encodes the amino acid sequence according to SEQ ID NO: 2 or biologically functional parts thereof, wherein said biologically functional parts have osteoinductive capabilities, and

(d) a nucleotide sequence which encodes the mature protein with amino acids 382-501 according to SEQ ID NO: 2,

to a patient in need of such treatment.

11. The method according to claim 10, further comprising administering a ~~matrix or other~~ carrier, diluent and/or filler along with said protein of the TGFβ family.

Cancel claims 12 and 13.

14. A method for inducing angiogenesis, comprising administering a protein of the TGFβ family, wherein said protein is encoded by a DNA molecule which comprises a sequence selected from the group consisting of:

(a) the sequence shown in SEQ ID NO: 1,

(b) a part of SEQ ID NO: 1 which ~~encodes~~ comprises nucleotides 1783-2142 and encodes the mature protein,

(c) a nucleotide sequence which encodes the amino acid sequence according to SEQ ID NO: 2 or biologically functional parts thereof, wherein said biologically functional parts have osteoinductive capabilities, and

(d) a nucleotide sequence which encodes the mature protein with amino acids 382-501 according to SEQ ID NO: 2,

to a patient in need of such treatment.

15. The method according to claim 14, further comprising administering a ~~matrix or other~~ carrier, diluent and/or filler along with said protein of the TGFβ family.

Cancel claims 18–21.

22. The method according to claim 6, further comprising administering a ~~matrix or other~~ carrier, diluent and/or filler along with said protein of the TGFβ family.

IN THE SPECIFICATION:

On page 4, replace the last paragraph with the following paragraph:

~~Figure1~~FIG. 1A-1B shows a comparison between the amino acid sequence of MP-52 and several members of the BMP protein family starting with the first of the seven conserved cysteine residues. * denotes that the amino acid is the same in all compared proteins; + denotes that the amino acid corresponds in at least one of the proteins compared to MP-52.

On page 5, replace the first paragraph with the following paragraph:

~~Figure 2~~FIG. 2A-2B shows the nucleotide sequences of the oligonucleotide primers that were used in the present invention and a comparison of these sequences with known members of the TGFβ family. M denotes A or C, S denotes C or G, R denotes A or G and K denotes G or T. 2a shows the sequence of the primer OD, 2b shows the sequence of the primer OID.

On page 5, insert the following paragraphs after the first paragraph:

FIG. 3 discloses a Western blot indicating the production of MP52 using vaccinia viruses as expression systems.

FIG. 4 discloses a schematic view of the plasmid pABWN.

FIG. 5 discloses a section of an implant (matrix-bound MP52, 26 days after implantation) stained according to von Kossa. Mineralized tissue in black is clearly distinguished from the surrounding muscle tissue.

FIG. 6 discloses a partial cross-section view of the implant of FIG. 5, but stained according to Masson-Goldner.

Replace the paragraph bridging pages 13-14 with the following paragraph:

The clone was completed up to the 3' end of the cDNA according to the method described in detail by Frohmann (Amplifications, published by Perkin-Elmer Corp., Issue 5 (1990), pp 11-15). The same embryonic mRNA that had been used to isolate the first fragment of MP-52 was reversally transcribed as described above. The amplification was carried out using the adapter primer (AGAATTCGCATGCCATGGTCGACG) (SEQ ID NO:3) and an internal primer (CTTGAGTACGAGGCTTTCCACTG) (SEQ ID NO: 4) of the MP-52 sequence. The amplification products were reamplified using an overlapping adapter primer (ATTCGCATGCCATGGTCGACGAAG) (SEQ ID NO:5) and an overlapping internal primer (GGAGCCCACGAATCATGCAGTCA) (SEQ ID NO:6) of the MP-

52 sequence. After restriction cleavage with NcoI the reamplification products were cloned and sequenced Into a vector that was cleaved in the same way (pUC 19 (Pharmacia No. 27-4951-01) having a modified multiple cloning site which contains a single NcoI restriction site) and sequenced. The clones were characterized by their sequence overlapping at the 3' end of the known MP-52 sequence. One of these was used as a probe to screen a human genomic gene bank (Stratagene No. 946203) according to a method described in detail by Ausubel et al. (Current Protocols in Molecular Biology, published by Greene Publishing Associates and Wiley-Interscience (1989)). One phage (λ 2.7.4) was Isolated from 8 x 10^5 λ phages which contained an insertion of about 20 kb and which is deposited at the DSM under the depository number 7387. This clone contains further sequence information at the 5' end in addition to the sequence isolated from mRNA by the described amplification methods.

Replace the paragraph bridging pages 14-15 with the following paragraph:

The genomic DNA contains an intron of about 2 kb between base pairs 1270 and 1271 of SEQ ID NO:1. The sequence of the intron is not shown. The correctness of the splicing site was confirmed by sequencing an amplification product which was derived from cDNA containing this region. These sequence informations were obtained using a slightly modified method which is described in detail by Frohmann (Amplifications, published by Perkin-Elmer Corporation, Issue 5

(1990), pp 11-15). The same embryonic RNA that was also used to isolate the 3' end of MP-52 was reverse transcribed using an internal primer orientated in the 5' direction of the MP-52 sequence (ACAGCAGGTGGGTGGTGTGGACT) (SEQ ID NO:7). A polyA tail was attached to the 5' end of the first cDNA strand using terminal transferase. A two-step amplification was carried out, firstly by using a primer composed of oligo dT and an adapter sequence (AGAATTCGCATGCCATGGTCGACGAAGC(T16)) (SEQ ID NO:8) and secondly an adapter primer (AGAATTCGCATGCCATGGTCGACG) (SEQ ID NO:3) and an internal primer (CCAGCAGCCCATCCTTCTCC) (SEQ ID NO:9) from the MP-52 sequence. The amplification products were reamplified using the same adapter primer and an overlapping internal primer (TCCAGGGCACTAATGTCAAACACG) (SEQ ID NO:10) from the MP-52 sequence. Subsequently the reamplification products were reamplified using an overlapping adapter primer (ATTCGCATGCCATGGTCGACGAAG) (SEQ ID ON:5) and an overlapping internal primer (ACTAATGTCAAACACGTACCTCTG) (SEQ ID NO:11) from the MP-52 sequence. The final reamplification products were cloned with blunt ends into a vector (Bluescript SK, Stratagene No. 212206) which had been cleaved with EcoRV. The clones were characterized by their sequence overlapping with the DNA of λ 2.7.4.

Replace the paragraph bridging pages 21-22 with the following paragraph:

For this the HindIII fragment from plasmid pSK52s that starts with nucleotide 576 in SEQ ID NO. 1, was isolated and the protruding ends were made blunt by treatment with Klenow fragment. A Not I restriction cleavage site was introduced at both ends of the fragment by ligation of the adapter.

Adapter: AGCGGCCGCT (SEQ ID NO:12)

TCGCCGGCGA (SEQ ID NO: 41)

Vector pABWN was restricted with XhoI, also treated with the Klenow fragment and dephosphorylated with intestinal alkaline phosphatase from the calf (Boehringer Mannheim). The same phosphorylated adapter was ligated on so that an insertion of the MP52 fragment after restriction with NotI into the generated Not I cleavage site of the vector was now possible. The expression vector that results is subsequently denoted HindIII-MP52/pABWN. All the reactions carried out for the cloning were carried out according to standard methods (e.g. CP units 3.16).

Election/Restrictions

Claims 6, 10, 11, 14, 15 and 22 are allowable. The restriction requirement between the species, as set forth in the Office action mailed on 12/13/2007, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Claims 12 and 13, directed to the treatment of osteoporosis or arthrosis are no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
AUGUST 3, 2009